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Award Number: W81XWH-14-1-0020

TITLE: A SOF Damage Control Resuscitation Cocktail

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REPORT DATE: May 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

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W81XWH-14-1-0020: A SOF Damage Control Resuscitation Cocktail: Year 1 Project Report

Nathan White MD University of Washington Seattle, WA, USA

INTRODUCTION

Executive Summary: The goal of this project is to develop a new damage control resuscitation (DCR) cocktail for use by SOF's that is capable of improving survival from polytrauma in austere settings. The cocktail components include Hextend for volume resuscitation and tissue perfusion, fibrinogen concentrate for hemostasis, and tranexamic acid for hemostasis. These components are tested in a combat-relevant swine polytrauma model of hemorrhagic shock with traumatic brain injury, free internal bleeding from an aortic tear, and femur fracture. Model development and validation, and objective 1 and 2 have been initiated in year 1 with an official project start date of April 15, 2014. The project has met with one primary scientific hurdle which has been overcome by adding vasopressin to the model to encourage more bleeding. We expect completion of this project to be on time and within budget.

BODY

Scientific Issues: Due to severe injury and the presence of traumatic brain injury, neurovascular responses to Hextend bolus were found to be blunted. Blood pressure did not increase in response to the Hextend bolus similarly to that observed in previous simple hemorrhage models. The lack of blood pressure increase during fluid bolus

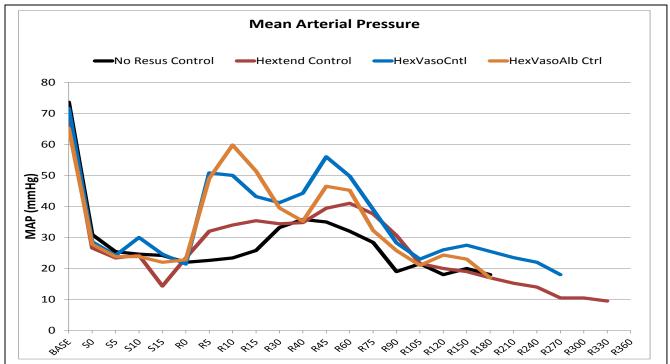
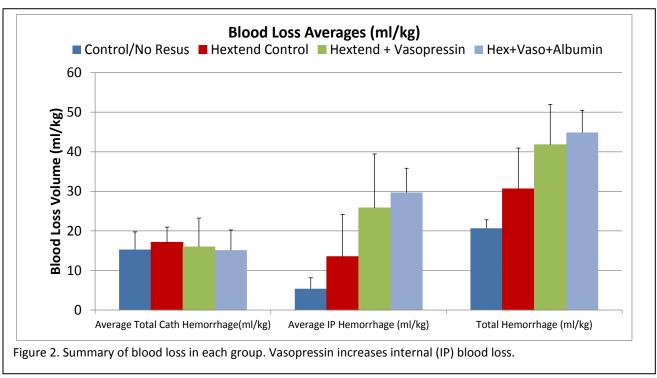


Figure 1. Mean arterial pressure response to bleeding and fluid bolus. The addition of vasopressin improves blood pressure response to fluid bolus.

would not allow adequate blood loss from the aortic tear, preventing testing of fibrinogen and tranexamic acid as hemostatic agents. Therefore, a change in the model was required. Namely, small dose vasopressin was added to each fluid bolus to support neurovascular tone, which encouraged blood pressure rise during fluid bolus, and increased internal bleeding now suitable for hemostatic testing. (**Figures 1 and 2**) The model, including vasopressin, is now suitable for testing of the full DCR cocktail which is now underway.

KEY RESEARCH ACCOMPLISHMENTS



Model Initiation and Development: Model development has been completed and the model is now performing as predicted after the addition of vasopressin to fluid resuscitation. Animals treated with vasopressin tend to spike their blood pressure, rebleed, and expire very quickly. Survival curves are shown in Figure 3. The model is now performing sufficiently in order to adequately test the hypotheses that fibrinogen concentrate and TXA can decrease blood loss and extend survival time during DCR of polytrauma.



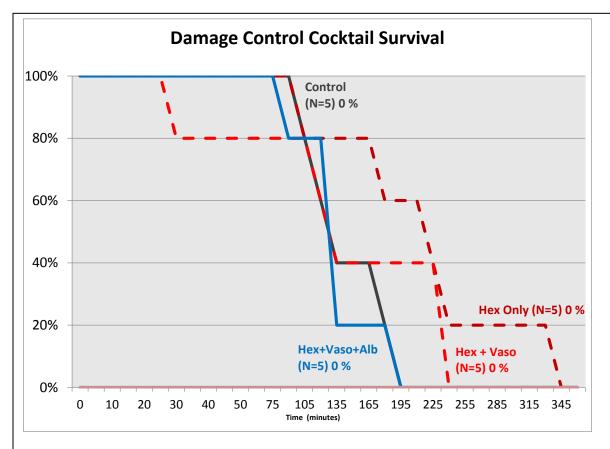


Figure 1. Survival curves for each control arm. The addition of vasopressin causes earlier death due to increased internal hemorrhage.

REPORTABLE OUTCOMES

Objectives

- Fibrinogen Concentrate Dose Titration (underway): The goal of objective 1 is
 to determine an appropriate dose of human fibrinogen concentrate (Riastap™,
 CSL Behring) needed to reduce blood loss and extend survival in this model.
 Due to the addition of vasopressin to the protocol, we now require 2 control arms
 and must reduce the number of fibrinogen concentrations tested from 3 to 2.
 - Negative Control: No fluid resuscitation. (N=5/5 complete)
 - **Hextend Control:** Hextend (7ml/kg+3ml/kg Normal Saline volume control) given as two boluses separated by 30 minutes (N=5/8 complete).
 - Hextend + Vasopressin Control: Hextend + 0.4ug/kg Vasopressin given as two boluses separated by 30 minutes (N=5/8 complete).
 - Hextend + Vasopressin + <u>High-Dose Fibrinogen</u> (200mg/kg total): Hextend + Vasopressin + Fibrinogen 100mg/kg given as two boluses separated by 30 minutes (N=0/8 complete).

- Hextend + Vasopressin + <u>Low Dose Fibrinogen</u> (50mg/kg total): fibrinogen given as two 25mg/kg boluses separated by 30 minutes (N=0/8 complete).
 - Results: Control arms with vasopressin are now exhibiting increased internal blood loss and short survival times. These parameters are now adequate for testing the hemostatic effects of fibrinogen concentrate and tranexamic acid.
- 2. Non-hemostatic protein control (underway): The goal is to determine the hemostatic contribution of fibrinogen concentrate to resuscitation aside from its general protein oncotic effects. The dosage of albumin is matched to the highest dosage of fibrinogen tested from Objective 1. The dosages are standardized by molar concentration of protein.
 - **Albumin Control:** Hextend+Vasopressin + Albumin (200mg/kg fibrinogen equivalent) given as two boluses separated by 30 minutes (N=5/8 completed).
 - Results: Five of eight experiments are complete. The survival and blood loss are not different than the Hextend+Vasopressin control group. These results suggest no nonspecific protein or oncotic effects of protein on resuscitation from polytrauma.
- 3. Objective 3 (to begin in year 2): Determine the effects of adding tranexamic acid (15mg/kg) alone and in combination with fibrinogen concentrate. The optimal concentration of fibrinogen determined in objective 1 will be used in these experiments where indicated. This objective has been changed by adding vasopressin to the DCR cocktail.
 - Tranexamic Acid Control: Hextend + Vasopressin + TXA given as two boluses separated by 30 minutes (N=0/8 complete)
 - Tranexamic Acid + Fibrinogen: (Hextend +Vasopressin + Fibrinogen + TXA given as two boluses separated by 30 minutes (N=0/8 complete)

Animal Use:

Updated animal use protocol was approved on 12-04-2014.

We have used a total of 31 of 128 allotted animals for this study.

Model Development: 11/25 animals

Objective 1: 15/29 animals

Objective 2. 5/8 animals

Objective 3. 0/16 animals

Projects	Months 1-3-April- June '14	Months 4-12, July'14-April'15		Months 13- 15, May- July'15	Months 16-22, Aug'15-Feb'16	Months 23-24, March-April'16
1.) Project Preparation:	ACURO Approval	Model Development				
Goal- Preparation for experiments.	Lab setup Acquire Animals	Protocol F 2 nd ACI Appro	URO			
2.) Objective 1: (Year 1:				FBG Dose Escalat	ion Study	
Months 4-12) Goal – Identify optimal fibrinogen concentration needed to augment low volume Hextend field resuscitation.			Data Analysis, Submit Year-1 report			
3.) Objective 2: (Year 2: Months 13-15) Goal-Albumin control experiments to determine the specific effect of fibrinogen.			Albumin Cont	rol Experiments	Data Analysis supplementa Report, and Lab Resupply and setup	
4.) Objective 3: (Year 2: Months 16-22) Determine effect of adding tranexamic acid (15mg/kg) to the optimal fibrinogen dosage determined in objective 1.					TXA Dose Experiments	
Study Close (Year 2: Months 23-24). Final Report to USSOCOM, Final publication						Data Analysis and Publication

CONCLUSIONS

Model development is complete and testing of the resuscitation cocktail is underway. The problem of lack of bleeding has been solved by the addition of vasopressin to the model. We expect the project to be completed on time and within budget.